THE INFLUENCE OF BIHEMISPHERIC TRANSCRANIAL DIRECT CURRENT STIMULATION ON MUSCLE FATIGUE

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Bachelor of Science – Neuroscience
University of Rochester
2021

A thesis submitted in partial fulfillment
of the requirements for the

Master of Science – Kinesiology

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University of Nevada, Las Vegas
May 2024

UNLV | GRADUATE COLLEGE

Thesis Approval

The Graduate College
The University of Nevada, Las Vegas

March 25, 2024

This thesis prepared by

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entitled

The Influence of Bihemispheric Transcranial Direct Current Stimulation on Muscle Fatigue

is approved in partial fulfillment of the requirements for the degree of

Master of Science – Kinesiology
Department of Kinesiology and Nutrition Sciences

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ABSTRACT

Unilateral transcranial direct current stimulation (tDCS) using two electrodes placed over the primary motor cortex (M1) and the contralateral supraorbital (SO) region (M1-SO montage) has been shown to decrease the progression of muscle fatigue. The primary purpose was to determine the impact of bihemispheric tDCS (bi-tDCS) applied over the left and right M1s (bi-tDCS) on the time to task failure (TTF) of a precision-grip task. The study implemented a double-blind, randomized, SHAM-controlled, within-subjects design. A total of 20 participants performed two experimental sessions (bi-tDCS and SHAM conditions) separated by a one-week washout. During each experimental session, a fatiguing isometric contraction of the right hand was performed with a precision grip during concurrent application of either bi-tDCS or SHAM stimulation of the two M1s. The fatiguing contraction required participants to match a target force equal to 15% of their maximum voluntary contraction (MVC) force until TTF. The main findings were that there were no statistically significant differences in TTF ($P = 0.730$) and percentage decline in MVC force ($P = 0.733$) between the bi-tDCS and SHAM conditions. Furthermore, there were no significant differences in force error, standard deviation of force, or EMG activity between the two conditions. These results indicate that bi-tDCS does not delay the progression of fatigue during a precision grip task in healthy adults in the task conditions of the current study.

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CHAPTER 1

INTRODUCTION

Muscle fatigue can be described as a decline in the maximum voluntary force-generating capacity of muscle due to exercise [1-3]. Common observation indicates that fatigue can impact every aspect of human motor behavior. For example, it is well-established that fatigue leads to increases in motor output variability [4], decreases in movement accuracy [5], and decreases in maximum force production [6]. Accordingly, significant research efforts have been made for over a century to determine the physiological mechanisms underlying fatigue and strategies to attenuate the negative impacts of fatigue on motor performance [1]. One major outcome of these studies is that the motor task parameters (e.g., intensity and type of muscle contraction, total active muscle mass, load type, target muscles, exercise duration) determine the relative contribution of the physiological factors responsible for the development of fatigue and eventually cessation of exercise [7, 8]. Thus, a common approach has been to categorize the processes contributing to fatigue into either central (neural) factors that occur within the central nervous system at the levels of the cortex, brain stem, and spinal cord; or peripheral (muscular) factors that occur at or distal to the neuromuscular junction [1, 2].

During a fatiguing contraction, a number of neural adjustments occur, such as increased output by the primary motor cortex (M1) to motor neurons, in order to recruit more motor units to sustain the requisite level of force [1-3, 7, 8]. In addition, there are enhancements in motor unit discharge rate variability, decreases in discharge rates of some motor units [3, 7], and greater frequencies of transient electromyographic (EMG) bursts [9]. Major afferent feedback-related alterations include reductions in Ia afferent excitatory feedback to motor neurons and enhancements in group III and IV afferent inhibitory inputs to motor neurons and supraspinal

sites [7, 10]. These neural changes are most prominent during submaximal isometric fatiguing contractions at low levels (e.g., 10-20%) of maximal voluntary contraction (MVC) force, which comprise the task conditions that are most commonly employed in fatigue studies [3, 11]. Accordingly, research has shown that about 50–66% of the total fatiguability under these conditions is due to supraspinal mechanisms. In contrast, during sustained MVC tasks, only about 25% of the fatiguability is due to supraspinal adjustments, as most of the remaining contribution is due to changes that occur at the level of the muscle [2, 10].

Despite these insights gained over decades of fatigue research, there are a surprisingly small number of interventions available that can meaningfully delay the progression of fatigue and mitigate its negative effects on motor performance. Long-established physical training methodologies that incorporate the principles of specificity (training under fatigue) and progressive overload are effective and form the foundation of fatigue attenuation strategies. In addition, the utilization of certain nutritional practices [12], dietary supplement approaches [13, 14], and even prescription-based pharmacological agents [2, 11] have shown efficacy. Nonetheless, these types of established longstanding interventions are either already well-known, applicable to only certain types of motor tasks, work only in select environments, can be difficult to put into widespread use, or have potential negative side effects. Therefore, new adjunct interventions that could delay the manifestation of fatigue would have substantial biomedical and clinical significance, given the impact of fatigue on human motor performance in both healthy populations and in numerous disease states [15].

Non-invasive brain stimulation methods have been increasingly investigated over the past 15–20 years and may represent a safe, efficacious, and cost-effective adjunct class of interventions to improve several aspects of human motor performance [16-21]. Transcranial

direct current stimulation (tDCS) has been not only the most frequently studied non-invasive brain stimulation method but also the most effective and practical for widespread utilization. The vast majority of such studies have focused on the application of tDCS for motor skill and motor learning applications. In general, the most consistent findings in the collective literature on these topics indicate that a 20-minute session of tDCS delivered to M1 with a current strength of 1–2 mA during task practice can augment motor skill to a greater extent (~10–15%) than a SHAM stimulation (practice alone) [16, 22-24]. This has been most frequently accomplished by using two electrodes (anode, cathode) that are placed over M1 and the contralateral supraorbital (SO) region (M1-SO montage), respectively. Furthermore, these parameters of stimulation usually also result in enhancements in the excitability and plasticity of M1, which may be at least one of the mechanisms responsible for the observed effects on motor skill. Interestingly, a non-trivial number of studies have reported that tDCS applied to M1 can delay muscle fatigue and extend the time to task failure (TTF) [11, 25-28], although these studies are much fewer in number compared with tDCS motor skill studies. Accordingly, several reviews of the literature [29-31] have concluded that the preponderance of the available evidence indicates that tDCS delivered with a SO-M1 montage significantly lengthens the endurance time or the TTF of a variety of motor tasks. However, two of these systematic reviews and meta-analyses concluded that these positive tDCS outcomes should be considered small to moderate in magnitude [29, 31].

Since the publication of the initial encouraging tDCS studies on motor skill and muscle fatigue, there have been considerable efforts to find ways to further augment the positive outcomes associated with tDCS application. These improvements were thought to be highly probable because tDCS was in the early developmental stages, and there are an exceedingly large number of possible stimulation parameter combinations that could be implemented. Some of

these have included alterations in the timing of tDCS relative to motor task execution (before versus during) along with the modulations of various tDCS parameters such as stimulation duration, current strength, and brain area targeted, to name a few. In addition, different electrode montage configurations and characteristics were investigated and compared to the established SO-M1 montage. One of the earliest and most promising montages involved placing the anode in the same location as in the SO-M1 montage (e.g., left M1), but with the cathode placed over the contralateral M1 (e.g., right M1) instead of the SO [32]. In this specific example, the rationale for this bihemispheric montage was based on the interhemispheric competition model that postulates that there is competition between the two M1s during unilateral movements. Therefore, placement of the cathode over the right M1 would inhibit it and reduce the amount of interhemispheric inhibition exerted on the left M1. This outcome coupled with the further increase in excitation of left M1 due to the anode placed over it, would result in greater left M1 excitation and greater motor performance gains of the right hand when compared with the SO-M1 montage. Accordingly, Naros et al. [33] performed a direct comparison study and found that this bihemispheric electrode montage (hereafter referred to as bi-tDCS) resulted in greater motor learning compared to the SO-M1 montage. Consistent with this finding, a systematic review and meta-analysis concluded that bi-tDCS induced greater motor learning compared to unilateral tDCS (SO-M1 montage) in studies involving healthy adult populations [34]. These findings were further supported by an extensive study by Waters et al. (2017) that reported greater skill learning in a bi-tDCS group versus a unilateral tDCS group in a 5-finger sequence task paradigm [35]. However, the authors concluded, based on both behavioral and fMRI data, that the effects of bi-tDCS were inconsistent with the interhemispheric competition model. Instead, they proposed an interhemispheric cooperation model that proposed that superior bi-tDCS effects

were due to the induction of plasticity in both hemispheres, which led to better cooperation between the left and right M1s when executing motor tasks [35]. Collectively, these results suggest that it is theoretically plausible that a bi-tDCS montage could also elicit even greater positive effects on the attenuation of muscle fatigue than those that have been observed in fatigue studies utilizing the SO-M1 montage.

The primary purpose of the present study was to determine the impact of bi-tDCS applied over the left and right M1s on the TTF of a precision grip task. The secondary purpose was to determine some of the physiological mechanisms underlying any observed increases in TTF due to bi-tDCS application. These purposes were accomplished by requiring participants to perform a sustained isometric fatiguing contraction in a bi-tDCS condition and a SHAM condition on two different days separated by a washout period of one week. In addition, the fatiguing contractions were performed simultaneously with stimulation while measurements of EMG activity, force, error, and force variability were collected. It was hypothesized that: 1) bi-tDCS delivered to the left and right M1s would prolong the TTF of the fatiguing contraction and reduce the magnitude of decline (% change) in pre- to post-MVC force compared to SHAM stimulation; 2) the rate of increase in EMG in the fatiguing contraction would be lower in the bi-tDCS condition in comparison to the SHAM condition; and 3) the rate of increase in force error and standard deviation (SD) of force in the fatiguing contraction would be lower in the bi-tDCS condition in comparison to the SHAM condition. These predictions were collectively based on prior M1-tDCS motor skill and fatigue studies that employed the SO-M1 electrode montage as well as the findings of several investigations that reported that the bi-tDCS montage could enhance motor skill to a greater degree than the traditional M1-SO montage when targeting M1.

CHAPTER 2

METHODS

Participants

A total of 20 healthy adults (10 males, 10 females; mean age: 25.5 ± 6.8 SD) gave written informed consent and completed the study. Participants were required to be right-handed as indicated by the laterality quotient (mean: 0.88) of the Edinburgh Handedness Inventory [36]. In addition, participants were free of any neurological disorders, psychiatric conditions, migraine histories, and uncontrolled medical conditions. Finally, participants did not meet any of the exclusion criteria for non-invasive brain stimulation studies [37, 38]. The study protocol was approved by the Biomedical Institutional Review Board of the University of Nevada, Las Vegas (UNLV-2023-583) and all experimental procedures were consistent with the Declaration of Helsinki.

Experimental Design

The study implemented a double-blind, randomized, SHAM-controlled, within-subjects experimental design. All procedures involving motor tasks were performed with the right hand. A within-subjects design was selected primarily because there can be significant individual variability in the degree of responsiveness to tDCS. Specifically, there are wide ranges of anatomic, biological, physiological, and genetic features that can influence the amount of current reaching cortical neurons as well as other aspects of the susceptibility to stimulation (for reviews see [39, 40]). Therefore, these interindividual issues are mitigated by the within-subjects design. In addition, within-subjects designs allow for much greater statistical power when compared to between-subjects designs [41].

Experimental Procedures

Two experimental sessions were conducted in which each participant received either bi-tDCS or SHAM stimulation. The stimulation sessions were separated by a wash-out period of one week [42, 43]. The experimental condition (bi-tDCS or SHAM) was randomized using a commonly used online tool (Research Randomizer; www.randomizer.org). Overall, 10 participants completed active bi-tDCS followed by SHAM, and the other 10 completed SHAM followed by bi-tDCS application. In all sessions, the following experimental procedures were completed in the order prescribed: 1) pre-9-hole peg test (9-HPT); 2) the first dorsal interosseus (FDI) muscle motor "hotspot" location (left and right M1s) and resting motor threshold (RMT) in the left M1 were determined with transcranial magnetic stimulation (TMS); 3) pre-MVCs; 4) Bi-tDCS or SHAM stimulation was delivered for three minutes prior to and over the course of the fatiguing contraction; 5) post-MVCs; and 6) post-9-HPT. Therefore, the only difference between the two experimental sessions was the stimulation type (bi-tDCS, SHAM). The experimental protocol for the two sessions is shown below in Figure 1.

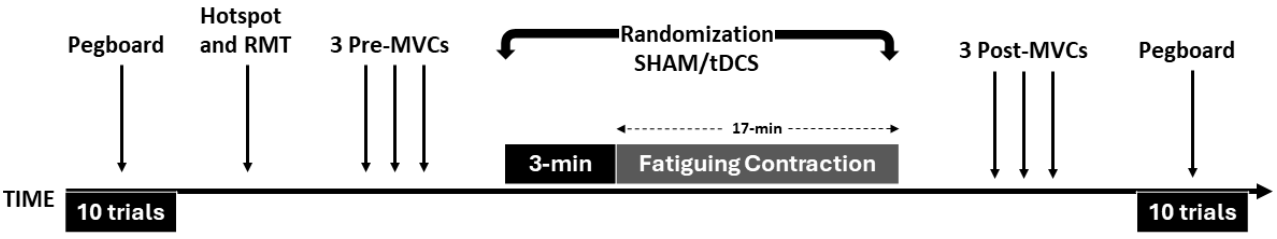

Figure 1. Schematic diagram of the study design and experimental protocol. Participants completed a bi-tDCS session and a SHAM session in a counterbalanced fashion. The fatiguing contractions were performed simultaneously with the stimulation conditions and were preceded by the pre-9-HPT assessment (10 trials), FDI motor hotspot locations and RMT determination via TMS, and pre-MVCs (three trials). Immediately following the fatiguing contractions, post-MVCs (three trials) and the post-9-HPT assessment (10 trials) were performed.

9-HPT. The Rolyan 9-HPT is an established standardized quantitative test of manual dexterity [44] and involves grabbing pegs with a precision grip and moving them using the upper limb from a dish to holes and back on a small device. It has several advantages over other manual dexterity inventories such as the ease and short amount of time in which it can be administered. Accordingly, it is included in the motor battery of the NIH toolbox [45]. The general 9-HPT testing procedures were performed similarly to a previous study [46] but with only the right hand. Briefly, the 9 pegs were removed from the dish of the 9-HPT one at a time, placed into the 9 holes on the other side of the dish, and removed and placed back in the dish. Most importantly, participants were instructed to perform the task as quickly and as accurately as possible. The time to complete the placement and removal of the 9 pegs was recorded for each trial. A total of 10 trials were performed both at the beginning and the end of the experimental session (Figure 1).

The 9-HPT was performed for two interrelated reasons. First, it was used as a transfer of motor skill test from the isometric precision grip task done in the fatiguing contraction. Second, it was used as a complementary metric of motor skill under fatigue to the metric of force error taken during the fatiguing contraction (see below). More specifically, if the TTF was lower in the bi-tDCS condition and this was accompanied by a lower force error compared with SHAM, it would provide at least partial evidence that bi-tDCS enhanced fatigue resistance through an effect on motor skill. Accordingly, a demonstration of increased 9-HPT performance after the fatiguing contraction in the bi-tDCS condition compared to SHAM would provide further evidence that any observed increases in TTF in the bi-tDCS condition could be at least partially due to enhancements in motor skill under fatigued conditions.

TMS Measures. For the TMS measurements, EMG electrodes were positioned in a belly tendon montage on the right FDI muscle of both the right and left hands. Motor-evoked potentials (MEPs) were measured in the respective FDIs in response to single-pulse TMS of both the left and right M1s. The motor hotspots for the right and left FDI muscles were identified using a Magstim 200^2 with a double 70 mm remote control figure-of-eight coil [47]. The TMS coil was placed against the surface of the scalp of each of the respective M1s with the handle directed backward and laterally. The coil was held tangentially to the scalp at an angle of 45 degrees from the midline, which produces a posterior-to-anterior directed current in the brain. A series of TMS pulses were delivered to the scalp until the location producing the largest MEP in the FDI muscle was identified. This location was marked with a non-permanent pen for the later measurement of RMT (left M1 only) and tDCS electrode placement (left and right M1s). RMT of the right FDI was quantified as the lowest TMS intensity as a percentage of the maximum stimulator output (% MSO) that elicited at least a MEP amplitude of 50 microvolts in five out of ten consecutive trials. The RMT was quantified for two reasons. First, it is a standard and simple measure of cortical excitability. Second, there is some evidence that individuals with lower RMT values have a greater response to tDCS [48, 49]. Thus, there could be an association between RMT and any observed increases in TTF in the bi-tDCS condition compared with the SHAM condition.

MVC Task. Three MVCs were completed before and after the fatiguing contraction utilizing established methods [50, 51]. Participants were seated and grasped a manipulandum using a precision grip. The grip manipulandum was located on a table surface and housed two separate force transducers. Thus, the index finger and thumb of the right hand were placed in opposition to each other and over the center of a transducer. The posture of the participant was

set with the hand semi-supinated, the upper arm abducted to about 45°, and the elbow flexed to about 90°. Participants were required to generate their maximum force in the shortest possible time at the onset of the contraction and to hold the maximum force attained for approximately 5 seconds. The force of the index finger and thumb was summed online by the software system and the total force was given as visual feedback to the participants on a large computer monitor. A one-minute rest period was enforced between all pre and post-MVC trials (Figure 1). Most importantly, the MVC trial that had the greatest force value of the three pre-MVC trials was identified as the pre-MVC. This force value was used to calculate the individual target force for the fatiguing contraction for each participant. In contrast, the first MVC executed after the fatiguing contraction was identified as the post-MVC. Thus, the force value during this MVC was utilized to quantify fatigue (percentage decline in MVC force from the pre- to the post-MVC). This first post-MVC was executed as fast as possible after the cessation of the fatiguing contraction. This could usually be accomplished within 10–15 seconds due to one of the investigators quickly resetting the computer for MVC measurement.

Bi-tDCS Application and Stimulation Parameters. Bi-tDCS was applied at a stimulation intensity (current strength) of 1 mA to the left and right M1s using a NeuroConn DC Stimulator Plus/MR. This was accomplished via two rubber electrodes (5 × 7 cm) that were placed in sponges that were soaked in saline solution. The anode was placed on the left M1 over the FDI motor hotspot that corresponded to the right contralateral hand, whereas the cathode was placed on the right M1 over the FDI motor hotspot that corresponded to the left contralateral hand. Thus, each of these electrodes was centered over the dot left from the temporary markings attained during the TMS measurements. This electrode configuration and set of stimulation parameters was based on the study by Naros et al. [33], which found that bi-tDCS elicited greater

performance effects compared with the SO-M1 montage. The bi-tDCS montage was also chosen based on the following observations: 1) bi-tDCS increased motor skill to a greater degree than a SO-M1 montage in a study that involved a direct comparison [33]; 2) bi-tDCS may induce plasticity in both hemispheres and lead to better cooperation between the left and right M1s when executing motor tasks [35]; and 3) a systematic review and meta-analysis concluded that bi-tDCS montages elicited greater motor learning and motor performance effects compared with unilateral tDCS montages [34].

Similar to previous studies that have chosen to apply tDCS during as opposed to before the fatiguing contraction [25, 26], it is important to note that the exact stimulation duration in the bi-tDCS condition necessarily varied due to each individual's TTF [25, 43]. However, the stimulation duration was never longer than the allotted set time of 20 minutes. This involved a priming phase of 3 minutes [43] before the commencement of the fatiguing contraction and the continuation of the stimulation until the TTF was reached (Figure 1). As a consequence, this led to somewhat different bi-tDCS application times due to the diversity of TTF values exhibited by the participants [25, 43]. Finally, the tDCS device operation and blinding during the experiments were carried out by an investigator who did not partake in the data collection. Accordingly, the members of the research team who were responsible for the data collection were blind to the experimental condition in all experiments in the same manner as previous studies [52, 53].

Fatiguing Contraction Task. For the fatiguing contraction, the same general experimental arrangement and precision grip task was employed as in the MVC task. In addition, the precision grip task was also the same as in previous fatigue [43] and motor skill studies [51, 53]. Participants were required to sustain an isometric contraction using a precision grip and maintain the same overall body posture for as long as possible until task failure. The target force was set

to 15% of the force achieved in the pre-MVC and was displayed as a black horizontal line on a monitor in front of the participants. In addition, a second line was placed at a force level of 90% of the target force as a tolerance limit for participants to try to never go below. The total force produced by the index finger and thumb was displayed as a red line on the screen so that the participants could endeavor to match the red line to the black target force line. Importantly, participants were instructed to match the red force trace to the target force line as accurately as possible for the entirety of the fatiguing contraction. Accordingly, the duration that the fatiguing contraction could be maintained was quantified as the TTF. The three termination criteria [6] for the fatiguing contraction were: 1) failure to keep the precision grip force above the 90% tolerance line for three consecutive seconds; 2) lack of ability to keep the same hand, forearm, upper limb, or whole-body posture during the trial despite verbal encouragement; and 3) a complete failure to maintain the contraction and the target force line. This is usually the most common form of termination in sustained isometric fatiguing contractions as most participants eventually give up and the force drops precipitously [43].

Data Analysis

All data were acquired using custom scripts in the Signal software package (CED, Cambridge UK). Offline data analysis was completed using a custom Python script (Fredericksburg, Virginia, USA) and Signal scripts. The primary outcomes were TTF and % decline in MVC between the pre- and post-MVCs. Secondary outcomes included RMT, Pre-MVC, and target force, with these variables being considered control measures because significant differences between the two conditions for those variables could be potential confounds. In contrast, secondary outcomes collected over the entire time course of the fatiguing contraction included the average force, average EMG, force error, and SD of force. In addition,

these outcomes were calculated separately in four equal epochs of time (E1, E2, E3, and E4) over the fatiguing contraction. These epochs corresponded to 0-25%, 26-50%, 51-75%, and 76-100% of the fatiguing contraction time for each participant, respectively.

As mentioned previously, RMT was determined as the minimal TMS intensity that could produce a MEP amplitude of at least 50 microvolts in five out of ten sequential trials. The Pre-MVC was taken as the highest MVC among the three pre-MVCs and the target force was 15% of the Pre-MVC in every experiment. TTF was quantified as the time in seconds that the fatiguing contraction could be performed until one of the task termination criteria was met. The percentage decline in MVC was calculated as the percent difference between the Pre-MVC and the first post-MVC and provided the fatigue index in each experiment [1]. The average force was calculated as the mean force generated over each of the four epochs of the fatiguing contraction. For EMG, the interference EMG of the right FDI muscle obtained in the pre-MVCs was rectified. Next, the greatest average rectified EMG obtained over the plateau phase for the three MVC trials was taken as the maximum EMG. Subsequently, the EMG values attained during each of the four epochs of the fatiguing contraction were rectified and normalized to the maximum EMG for each participant. Force error was calculated analogously to previous motor skill studies [51, 53] and a prior fatigue study [43]. Thus, the absolute value of the difference between the force produced and the target force at each sampling point was determined and these values were averaged over each of the four epochs of the fatiguing contraction. Finally, the SD of force was calculated as the SD of the force produced over each time epoch.

Statistical Analysis

The primary outcome measures of TTF and percentage decline in MVC were compared between the bi-tDCS and SHAM stimulation conditions with separate two-tailed paired *t*-tests.

Similarly, the secondary outcome measures of RMT, Pre-MVC, and target force were also compared between the two conditions with separate two-tailed paired t-tests. Conversely, the secondary outcomes of average force and, average EMG, force error, and SD of force were compared between the bi-tDCS and SHAM stimulation conditions and epochs with separate 2 condition (bi-tDCS, SHAM) x 4 epoch (E1, E2, E3, E4) within-subjects ANOVAs. Finally, the secondary outcome of the 9-HPT was analyzed with a 2 condition (bi-tDCS, SHAM) x 2 test (pre, post) within-subjects ANOVA. The significance level for the statistical tests was set to $P < 0.05$ and the data are displayed as the means ± the standard errors in the figures. Finally, the effect sizes are reported as Cohen's *d* and partial eta squared values for the *t*-tests and the ANOVAs, respectively.

CHAPTER 3

RESULTS

RMT, Pre-MVC, and Target Force

For the RMT, pre-MVC, and target force, the paired *t*-tests indicated that there were no statistically significant differences between the bi-tDCS and SHAM stimulation conditions (P = 0.578, d = 0.127, Figure 2A; P = 0.234, d = 0.275, Figure 2B; and P = 0.234, d = 0.275, Figure 2C; respectively).

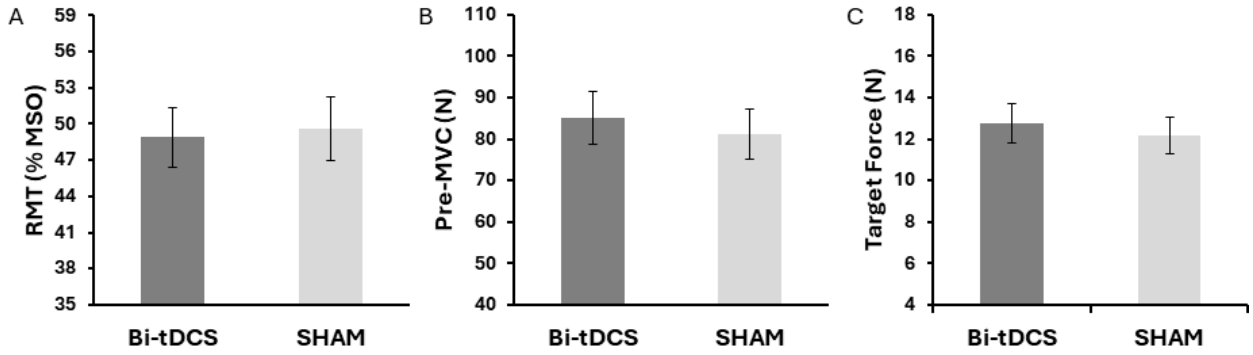

Figure 2. (A) RMT, (B) Pre-MVC, and (C) target force for the bi-tDCS and SHAM stimulation conditions.

TTF and % Decline in MVC Force

Paired *t*-tests indicated that there were no statistically significant differences between the bi-tDCS and SHAM stimulation conditions for the TTF (P = 0.730; d = 0.078; Figure 3A) or the percent decline in MVC (P = 0.733; d = 0.077; Figure 3B).

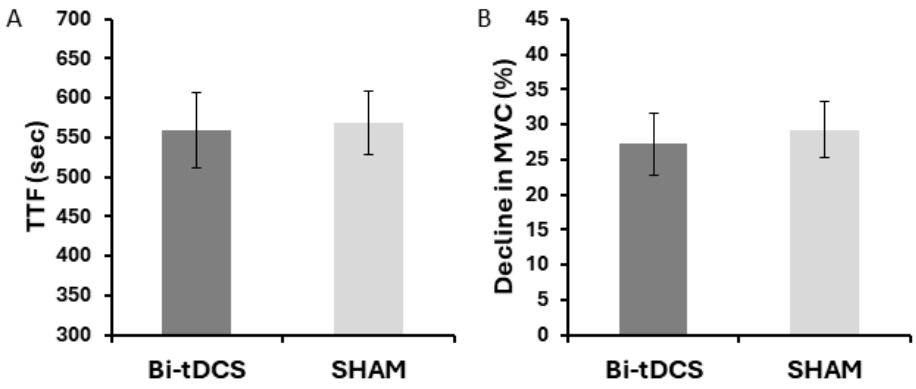

Figure 3. (A) TTF and (B) percentage decline in MVC force for the bi-tDCS and SHAM stimulation conditions.

Average Force and Average EMG during the Fatiguing Contraction

For average force, both the *condition* × *epoch* interaction ($P = 0.464$; $\eta_p^2 = 0.041$) and *condition* main effect ($P = 0.193$; $\eta_p^2 = 0.087$) were not statistically significant. There was a main effect for *epoch* ($P = 0.049$; $\eta_p^2 = 0.174$), however, none of the post hoc pairwise comparisons between epochs were statistically significant (P value range: 0.126 - 1; Figure 4A-B). For average EMG activity, both the main effect for *condition* ($P = 0.706$; $\eta_p^2 = 0.007$) and *condition* × *epoch* interaction ($P = 0.816$; $\eta_p^2 = 0.009$) were not statistically significant. However, there was a significant main effect for *epoch* ($P < 0.001$; $\eta_p^2 = 0.308$), as EMG rose gradually throughout the fatiguing contractions (Figure 4C-D).

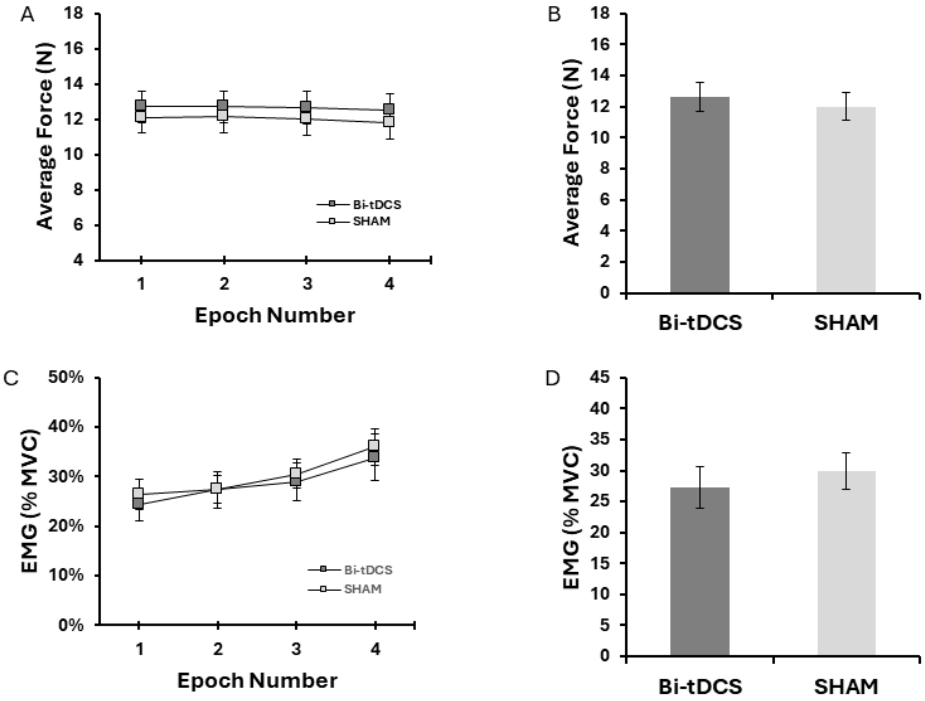

Figure 4. (A) The average force for the bi-tDCS and SHAM conditions across the four epochs, (B) the average force for the bi-tDCS and SHAM conditions when collapsed across epoch is shown for illustration purposes, (C) the average EMG for the bi-tDCS and SHAM conditions across the four time epochs, and (D) the average EMG for the bi-tDCS and SHAM conditions when collapsed across epoch is shown for illustration purposes.

Changes in Force Error and SD of Force with Time During Fatigue

For force error, both the main effect for *condition* ($P = 0.334$; $\eta_p^2 = 0.049$) and *condition* × *epoch* interaction ($P = 0.409$; $\eta_p^2 = 0.046$) were not statistically significant. However, there was a significant main effect for epoch ($P < 0.001$; $\eta_p^2 = 0.514$) as force error rose steadily during the fatiguing contractions (Figure 5A-B). For the SD of force, the main effect for *condition* ($P = 0.621$; $\eta_p^2 = 0.013$) and *condition* × *epoch* interaction ($P = 0.306$; $\eta_p^2 = 0.060$) were not statistically significant. However, there was a significant main effect for *epoch* ($P < 0.008$; $\eta_p^2 = 0.273$), as the SD of force increased progressively during the fatiguing contractions (Figure 5C–D).

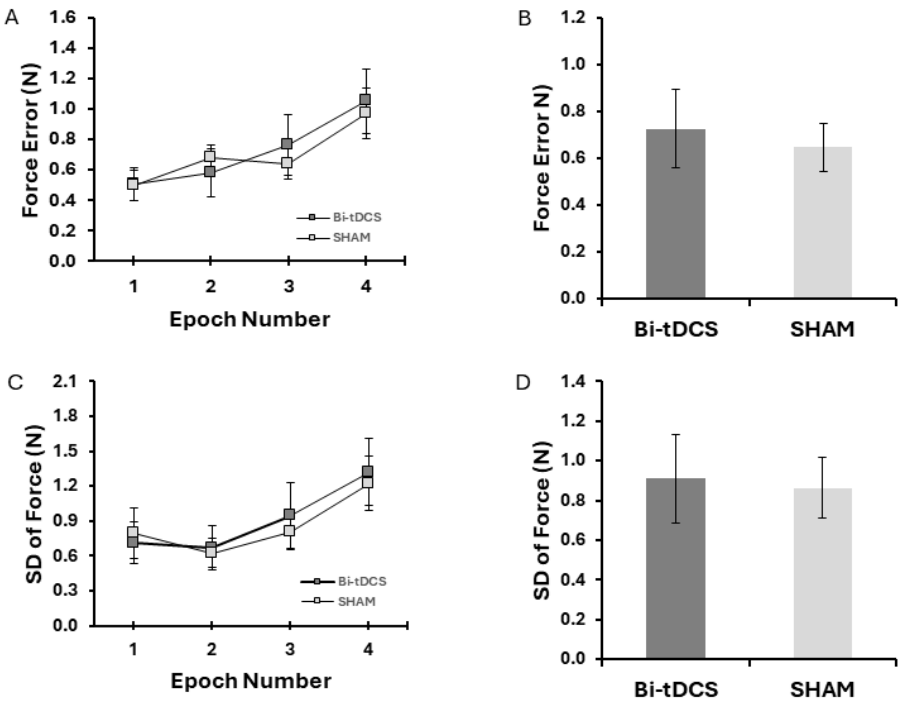

Figure 5. (A) The force error for the bi-tDCS and SHAM conditions across the four time epochs, (B) the force error for the bi-tDCS and SHAM conditions, when collapsed across epoch, is shown for illustration purposes, (C) the SD of force for the bi-tDCS and SHAM conditions across the four epochs, and (D) the SD of force for the bi-tDCS and SHAM conditions when collapsed across epoch is shown for illustration purposes. Force error and SD of force changes during fatigue for tDCS and SHAM conditions.

For the 9-HPT, the main effect for condition ($P = 0.485$; $\eta_p^2 = 0.026$), the main effect for *test* ($P = 0.657$; $\eta_p^2 = 0.011$), and the *condition* × *test* interaction ($P = 0.263$; $\eta_p^2 = 0.065$) were all not statistically significant (Figure 6).

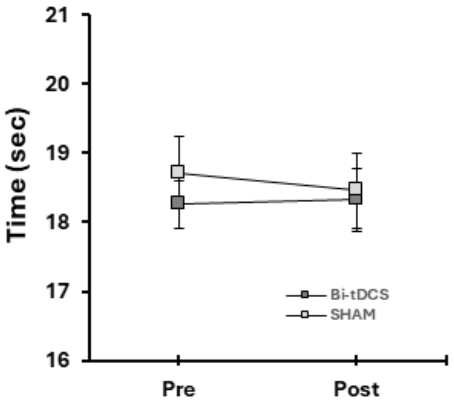

Figure 6. 9-HTP scores in the pre and post-tests for the bi-tDCS and SHAM conditions.

CHAPTER 4

DISCUSSION

The primary purpose of the current study was to determine the impact of bi-tDCS applied over the left and right M1s on the TTF of a precision grip task. The secondary purpose was to determine some of the physiological mechanisms underlying any observed increases in TTF due to bi-tDCS application. There were three sets of main findings: 1) the TTF and the percentage decline in MVC force values did not differ between the bi-tDCS and the SHAM stimulation conditions; 2) the increases in EMG activity, force error, and SD of force over the duration of the fatiguing contractions were similar between the bi-tDCS and SHAM stimulation conditions; and 3) the degree of transfer of motor skill under fatiguing conditions as assessed by the 9-HPT was similar for the bi-tDCS and SHAM conditions. Taken together, these results indicate that a single application of bi-tDCS delivered to the left and right M1s does not slow the progression of fatigue in a precision grip task in healthy young adults.

TTF and Percentage Decline in MVC Force Production

The present study seems to be the first to examine the effects of a bi-tDCS montage on the performance of a fatiguing contraction performed by muscles of the hand. This was accomplished by utilizing the most common and well-characterized fatigue experimental paradigm of a unilateral submaximal isometric fatiguing contraction of upper limb muscles [1–3]. These task parameters allow for strict experimental control and a greater ability to perform simultaneous behavioral and physiological measurements [11] compared with unconstrained full-body tasks involving anisometric contractions. In these experimental circumstances, the TTF and percentage decline in MVC force are usually the two primary outcomes used to characterize

the progression and magnitude of muscle fatigue, respectively. Thus, this study evaluated these measures when participants performed a fatiguing contraction concurrent with bi-tDCS or SHAM stimulation in two otherwise identical experimental sessions.

The a priori hypotheses were that bi-tDCS delivered to the left and right M1s would increase the TTF of the fatiguing contraction and reduce the magnitude of decline (percentage change) in pre- to post-MVC force compared to SHAM stimulation. In contrast to these two hypotheses, there was no statistical difference in the TTF and percent change (decline) in the MVC force between the two stimulation conditions. Thus, these observations indicate that bi-tDCS failed to significantly mitigate the progression of fatigue during the fatiguing contraction or the magnitude of fatigue exhibited immediately after task failure. Notably, these results were not due to factors such as the magnitude of the Pre-MVC and the associated calculations of target force as these values were almost equal between the b-tDCS and SHAM conditions. This is important because greater Pre-MVCs and target forces in one condition could have easily resulted in shorter TTF values in that condition. Furthermore, the average force generated across the entire fatiguing contraction as well as each of the four individual epochs did not differ between the two conditions. Thus, one condition did not exhibit a systematic bias whereby participants could have inadvertently or by chance produced a force that was on average slightly further below the target force line. Finally, the basic measure of cortical excitability of RMT at baseline was also similar across conditions. Taken together, the absence of significant differences in these task parameters and control measures indicates that the experimental design should have permitted the discrimination of differences in TTF and percentage decline in MVC if they had existed.

The current findings are not consistent with the preponderance of the available literature on the influence of tDCS on muscle fatigue and TTF. Furthermore, these studies have involved a variety of different motor tasks, muscle groups, stimulation parameters, and electrode montages. Nonetheless, a great number of these studies utilized the SO-M1 electrode montage and similar experimental paradigms (submaximal isometric contractions) as the present study [27-31, 54]. While to our knowledge there are no other bi-tDCS studies that involved muscle fatigue in the upper limb of young adults, the current findings are also in opposition with the vast majority of existing tDCS motor skill studies. Collectively, the vast majority of these studies have reported improved motor skill acquisition relative to SHAM when tDCS was delivered via a SO-M1 montage, especially during various types of precision and pinch grip tasks performed with the thumb and index finger [19, 20, 23]. In addition, the findings are also incongruent with a systematic review and meta-analysis [31] that reported greater positive effects with bi-tDCS compared to unilateral tDCS electrode montages, although this review comprised only motor learning studies, not fatigue studies. However, the current results do lend support to the observations of both tDCS motor learning [16] and fatigue investigations [29-31, 55] that have reported that a meaningful minority of tDCS studies have not reported performance enhancements. Most importantly, when tDCS has improved muscle fatigue resistance the overall effects have been small to moderate [29, 31]. These outcomes imply that tDCS does not always elicit significant enhancements in motor performance, especially regarding muscle fatigue resistance. Furthermore, the effects of tDCS could also be viewed as variable, not as effective as initially thought, and greatly dependent on individual responses to stimulation [11]. In summary, the current results suggest bi-tDCS application may not be an effective intervention to attenuate

muscle fatigue progression in healthy young populations, despite the theoretical advantages it likely offers compared to the SO-M1 electrode montage in motor skill studies.

EMG Activity and Force Modulations During the Fatiguing Contractions

When a submaximal isometric fatiguing contraction is sustained at a set target force level for as long as possible, there is always a progressive increase in the surface EMG amplitude of the muscles involved [1-3]. This is due to an increase in the recruitment of more motor units to maintain the required force and to a decrease in the conduction velocity of muscle fiber action potentials [56, 57]. In addition, there is also a concomitant increase in force error [43] and the SD of force throughout the course of fatiguing contractions [1, 3, 7, 8]. These behavioral changes primarily result from the aforementioned progressive and sometimes transient recruitment of larger motor units that have more muscle fibers than the already active smaller motor units, which results in greater deviations relative to the target force line. Thus, force error and force variability are progressively increased during sustained isometric fatiguing contractions, which is a universal observation in these experimental conditions.

It was originally predicted that the rate of rise in EMG activity, force error, and SD of force over the course of the fatiguing contraction would be lower in the bi-tDCS condition in comparison to the SHAM condition. This was based on several interrelated lines of reasoning. First, bi-tDCS application would be expected to increase cortical excitability, leading to a greater descending drive from M1 onto the motor neurons than would have been possible through voluntary activation alone, which would extend the TTF. Second, bi-tDCS could indirectly delay the progression of fatigue by eliciting acute online increases in motor skill. In the current experimental circumstances, this skill modification could result in an improved ability to match

the target force line more accurately. This should lead to more efficient force production and less work performed by the involved muscles. Thus, the deviations from the target line would be lower resulting in lower rates of rise in EMG activity, force error, and SD of force in the bi-tDCS condition. Third, it is plausible that bi-tDCS could lower pain perception, although this mechanism is less likely and was not a factor in the increased TTF observed in a previous fatigue study [58].

As expected, the FDI EMG, force error, and SD of force all exhibited a clear progressive increase during the fatiguing contractions. However, the rates of increase were very similar in the bi-tDCS and SHAM conditions. Thus, these results collectively suggest that there were comparable levels of cortical excitability, descending drive, and pain perception in the two conditions. In addition, the concomitant absence of a difference in accuracy (force error) during the fatiguing contraction and 9-HPT performance after the fatiguing contraction further supports these conclusions. This is because, in theory, increased cortical excitability should have led to increased motor skill during and after the fatiguing contraction in the bi-tDCS group if it were present. Regardless of the exact mechanisms, bi-tDCS neither increased force accuracy (reduced force error) during the fatiguing contraction nor elicited a transfer of motor skill effect after the fatiguing contraction as indicated by the 9-HPT scores. Overall, the findings suggest that bi-tDCS had no positive effects on the underlying physiological mechanisms that contribute to the that rates of rise of EMG, force error, and SD of force during fatiguing contractions.

Possible Reasons for the Lack of Bi-tDCS Effects on Fatigue Progression

The lack of effect of bi-tDCS on the progression of muscle fatigue was unexpected based on prior tDCS and muscle fatigue studies as well as research that has demonstrated the efficacy of b-tDCS in improving motor skill. In general, the possible mechanisms by which tDCS applied

to M1 could mitigate the progression of muscle fatigue and extend TTF were discussed above and in a recent literature review [34]. The two best candidate mechanisms of increased descending drive to motor neurons and increased motor skill, which would both be theoretically mediated by cortical excitability increases due to bi-tDCS, did not seem to occur. This was demonstrated by the rather basic behavioral (force error, SD of force, peg test) and physiological measures (rate of EMG rise) measures employed. To better determine the physiological underpinnings of the findings, concurrent measures of MEPs, cervicomedullary MEPs, Hoffman reflexes, and M-waves would have been required [11]. Nonetheless, the lack of differences between the bi-tDCS and SHAM conditions in all of the current dependent measures would make it extremely unlikely that any between condition differences would have emerged in these measures that would clarify the reasons for the negative findings of this study.

Despite the absence of extensive physiological measures, several factors could potentially explain the lack of significant bi-tDCS effects on muscle fatigue. The set of stimulation parameters (current strength, duration, timing) may not have been ideal for slowing the progression of muscle fatigue, notwithstanding their efficacy in numerous motor learning studies. In addition, one stimulation session might not have been adequate to induce significant effects on muscle fatigue, and therefore repeated bi-tDCS application over multiple days may be needed, at least based on motor skill studies [16, 19, 20]. On the other hand, the bulk of single day tDCS motor skill studies [16, 19, 20] and fatigue studies [29, 30] have been able to detect significant performance effects in one stimulation session. Third, the lack of significant bi-tDCS effects could have been due to ceiling effects as the participants were all healthy adults with an average age of 25.5 years. Accordingly, several studies by different research groups have shown that the magnitude of positive effects of tDCS on motor skill can be dependent on the initial

performance level of the individual [59, 60], the age of the participants (e.g., healthy old versus healthy older old adults) [61], and the extent of motor impairment due to disease [62]. Unfortunately, direct systematic comparison studies investigating this issue have not been conducted in fatigue conditions.

The factors identified above are among those often cited when tDCS does not lead to the expected increases in performance based on the majority of prior research. Some additional issues commonly cited in these cases, however, likely did not contribute to the current non-significant findings. For example, due to the implementation of a within-subjects design, variations in interindividual responses due to genetics, structural anatomy, and physiological characteristics [39, 40] were not applicable to the current investigation. Relatedly, the within-subjects design and the number of participants enrolled compared to the preponderance of tDCS studies [16] make the probability very low that issues related to sample size and statistical power meaningfully influenced the overall conclusions [41]. Accordingly, the Cohen's *d* and partial eta squared effect size values obtained in the present study in the bi-tDCS and SHAM condition comparisons were almost all small, and only a couple even reached the lower bounds of a moderate effect size.

Strengths and Limitations

The current study was conducted using a rigorous double-blind, randomized, SHAM-controlled, within-subjects design and the most common experimental paradigm for investigating muscle fatigue in neurophysiology studies. The study yielded results that were straightforward as all of the primary and secondary outcomes were almost indistinguishable between the bi-tDCS and SHAM conditions. Nevertheless, the study was subject to several limitations including a few of which contain a degree of overlap with the previously mentioned factors that could have

contributed to the lack of ability of bi-tDCS to mitigate muscle fatigue. Potential limitations could include: 1) only one current strength (1 mA) was used in a single session and this intensity of stimulation is at the lower end of the typical range of 1 – 2 mA. Nonetheless, this current level was decided upon as a starting point based on the most successful motor skill studies, although higher currents could plausibly be better for modulating fatigue. Thus, a current strength of 2 mA could have been more effective as has been seen or implied in some studies; 2) a more likely possibility is that the application of bi-tDCS before, as opposed to during, the fatiguing contraction could have been more efficacious. Support for this proposition comes from several tDCS studies that have shown greater TTF values compared to SHAM [27-31, 54], although tDCS applied during the contraction has also been successful [25, 26]; and 3) the low contraction intensity chosen for the target force level could have hindered the ability of bi-tDCS to exert an influence on muscle fatigue. This idea has some support from studies that have shown enhancements in a short series of MVCs [63] or in the total training volume of strength training sessions [64-66] at relatively high contraction intensities following tDCS. On the other hand, the previously mentioned findings that 50–66% of the total fatiguability observed in sustained submaximal isometric contractions is due to supraspinal factors. This would imply that the current experimental arrangement and contraction intensity should have been the most likely to find significant effects as all of the mechanisms of action of bi-tDCS should reside at supraspinal levels. Nevertheless, research involving sustained MVCs or using some of the established intermittent fatiguing contraction paradigms [6] at relatively high intensities is warranted in future bi-tDCS fatigue studies.

Conclusions

Bi-tDCS applied simultaneously with a submaximal isometric fatiguing contraction involving a precision grip task did not augment TTF to a greater extent than SHAM stimulation. Similarly, following the contraction, the percentage decline in MVC force observed was not significantly influenced by bi-tDCS. The absence of differences in these primary outcomes was accompanied by similar rates of increase for the secondary outcomes of average EMG, force error, and SD of force in the bi-tDCS and SHAM conditions. Collectively, these results indicate that bi-tDCS applied using the parameters of stimulation in the present study does not mitigate the progression of fatigue, at least in the current task conditions. In the future, research could investigate the impact of bi-tDCS on muscle fatigue over longer time periods (multiple days of stimulation) or using different stimulation parameters (current strengths, stimulation duration, timing relative to task performance. In addition, different brain areas could be targeted with bilateral or dual source tDCS electrode montages that have been shown to increase physical abilities such as maximal force production and motor skill in various populations.

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Education

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Professional Experience

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2021-2022	Clinical Research Associate Penn State Cancer Institute
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2019-2021	Emergency Department Research Associate Strong Memorial Hospital Rochester, NY
2021	Undergraduate Teaching Assistant School of Arts and Science Neuroscience Department: Applied Statistics University of Rochester
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Leadership Experience

2021-2022	Communications Pillar Chair Rise-Up Committee Penn State Cancer Institute
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